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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,898	MORRIS ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49,56-63,67-72 and 75-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49,56-63,67-72 and 75-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/5/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant cancels claim 66.

Accordingly, group K, claims 49, 56-63, 67-72, 75-86, diagnosis of colon cancer, by detecting the level of the nucleic acid SEQ ID NO:150, SEQ ID NO:152, and/or SEQ ID NO:154, are examined in the instant application.

The embodiment of claims 49, 56-63, 67-72, 75-86, as drawn to: 1) a method for diagnosis of colon cancer, by detecting the level of the protein encoded by the nucleic acid SEQ ID NO:150, SEQ ID NO:152, and/or SEQ ID NO:154, and 2) a method for diagnosis of stomach or prostate cancer, has been withdrawn from consideration as being drawn to non-elected invention.

Withdrawn Rejection

The 112, second paragraph rejection has been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 85 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons already of record in paper of 12/05/08.

The response asserts as follows:

The specification provides sufficient support to satisfy the written description requirement under section 112, first paragraph. For example, variants and methods of making such variants are described at paragraphs 0116-0136. These paragraphs describe, for example, sequence variants encoded by the claimed SEQ ID NOS and that such variants can be made by, for example, site-specific mutagenesis of nucleotides in the DNA encoding the CA protein using techniques well known in the art to produce DNA encoding the variant (Id. at para. 0116). Therefore, by describing the variants of the polypeptides, and that they can be made by changing the encoding nucleic acid, the application describes variants of the encoding nucleic acid. The variants fall into substitutions, insertions and deletions that can be prepared from mutagenesis of the encoding nucleic acid. Moreover, as described therein, the variants typically exhibit the same qualitative biological activity as the naturally occurring sequence. Chart 1 further sets forth specific substitutions of amino acids that can be introduced by incorporated into the encoding SEQ ID NOS. This description of a number of variants of encoded by SEQ ID NOS: 150, 152 and 154 is sufficient to satisfy the representative number of species articulated by the Examiner. Further, this description adequately describes the claimed invention such that one skilled in the art can recognize what is claimed. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The response has been considered but is not found to be persuasive for the following reasons:

The specification **does not describe structure** of the claimed at least 95% or 98% variants, wherein said variants have the function of threonine endopeptidase, nor structure of domains of SEQ ID NO: 150, SEQ ID NO:152 or SEQ ID NO:152 that are responsible for

threonine endopeptidase activity, or contribute to the three dimensional structure of SEQ ID NO: 150, SEQ ID NO:152 or SEQ ID NO:152 necessary for their function as threonine endopeptidase. One cannot predict that the claimed 95% or 98% variants would have the function of threonine endopeptidase, in view that protein chemistry is probably one of the most unpredictable areas of biotechnology, and such unpredictability applies as well to nucleic acids that encode proteins. Bowie (Science, 1990, 257:1306-1310) teaches that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie further teaches that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47

with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

Claims 49, 56-63, 67-72, 75-86 remain rejected under 35 U.S.C. 112, first paragraph, for lack of enablement for a method for diagnosis of colon cancer, comprising detecting differential level of the nucleic acid of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, or their at least 95% or 98% variants thereof, for reasons already of record in paper of 12/05/08.

The response asserts as follows:

Factors 1 and 2: The nature of the claimed invention and breadth of the claims.

Claims 49, 56 and 72 are directed to methods for diagnosing colon, stomach or prostate cancer by determining the difference in expression of a threonine endopeptidase encoding nucleic acid (SEQ ID NOS: 150, 152 and 154) in colon, stomach or prostate cancer tissue compared to non-cancerous colon, stomach or prostate tissue.. Claim 61 is similarly compares the difference in expression of proteasome component C7-I expression.

As taught by the specification, the use of oncogenic retroviruses --whose sequences insert into the genome of the host organism and result in cancer-- has allowed the identification of host cancer related sequences such as threonine endopeptidase, defined as a cancer associated (CA) gene or nucleic acid sequence. See the specification at paragraphs 0027-0031, 0287 and Example 1, paragraph 298. In this regard, the specification teaches the use of three mammalian

retroviurses (i.e., FeLV, MLV and MMTV) for tagging and identifying protooncogenes. See paragraph 0027, and paragraph 298. The specification describes that the integration of provirus affects the expression of host genes at or near the site of integration - a phenomenon known as retroviral insertional mutagenesis. See paragraph 0049. Possible changes in the expression of host cell genes due to insertional mutagenesis are taught to include: (i) increased expression of genes near the site of integration, (ii) decreased expression of genes due to functional inactivation caused by the integration, or (iii) expression of a mutated protein that has a different activity to the normal protein. See paragraph 49, lines 7-12.

The specification also teaches that differential expression of the CA genes such as threonine endopeptidase can be used for diagnosis of cancer or detection of cancer phenotype. See paragraph 0161. As will be discussed below, the specification further provides information about various means by which the differential expression of CA genes (including their mRNAs and proteins) can be determined. See Paragraphs 0074-0133. Thus, the present specification teaches that the differential expression of threonine endopeptidase encoding nucleic acids comprising SEQ ID NOs: 150, 152 and 154 can be used as claimed for diagnosis of cancer.

The response has been considered but is not found to be persuasive for the following reasons:

The claims 49, 56-59, 61-63, 67-72, 75-86 are drawn to a method for **diagnosing colon cance**r, comprising detecting **differential level** of the nucleic acid of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, or a genus of at least **95% or 98% variants** thereof in colon cancer tissue as compared to that of non-cancerous colon tissue. The claim 60 is drawn to detection of predisposition or **risk of colon cancer**, comprising detecting differential level of the

nucleic acid of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, or a genus of at least 95% or 98% variants thereof in colon cancer tissue as compared to that of non-cancerous colon tissue.

The claims are broad, encompassing not only detecting in colon cancer tissue or in colon tissue of a patient at risk of colon cancer, as compared to that of non-cancerous colon tissue, a differential level of the nucleic acid of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, but also a differential level of a genus of at least 95% or 98% variants thereof, with unknown structure and function.

The specification, however, does not have any data or objective evidence that the nucleic acid of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, or a genus of at least 95% or 98% variants thereof differentially express in colon cancer tissue or in colon tissue of a patient at risk of colon cancer, as compared to non-cancerous colon tissue. There are not data or objective evidence from retroviruse tagging indicating the nucleic acid of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, or a genus of at least 95% or 98% variants thereof differentially express in colon cancer tissue, or in colon tissue of a patient at risk of colon cancer, as compared to non-cancerous colon tissue.

Further, the specification does not teach how to make the claimed genus of at least 95% or 98% variants such that they have the same property, or the same function such as threonine endopeptidase, as that of SEQ ID NO:150, SEQ ID NO: 152 and SEQ ID NO: 154.

The response asserts as follows:

Factors 3 and 4." The relative skill in the art and the state of the prior art.

Applicants submit that the specification teaches one skilled in the art that the claimed sequences are sufficient to be predictive of colon, stomach or prostate cancer. As described above, the specification discloses that threonine endopeptidase encoding nucleic acid sequences SEQ ID NOS: 150, 152 and 154 were discovered through the retroviral insertional mutagenesis as a marker for diagnosis of cancer. The specification teaches that the product of a CA gene such as threonine endopeptidase can be a marker for cancer diagnosis, when the gene expression is differentially altered in a tissue as compared to a control such as non-cancerous colon, stomach or prostate tissue or such tissue isolated from a healthy individual. See paragraphs 0017 and 161. The end point for which the threonine endopeptidase is to be a marker is measured, according to the specification, by differential expression that is defined and quantified in terms of up- or down-regulation. See paragraphs 0051 and 0052. The specification further establishes the range of threonine endopeptidase gene product variability in terms of, for example, sequence homology (of least 95% to threonine endopeptidase mRNA) or hybridization at stringent condition (of e.g., 60° C in 5X SSC). See paragraph 0065 and 0071. The specification further describes means for determining sequence homology in paragraphs 0066-0069 and provides detail disclosure for hybridization conditions in paragraphs 0071-0072. The specification also provides information about the biological samples which can be used for detecting the CA gene expression and diagnosing cancer. See paragraph 0278. The specification teaches that, for example, laser capture microdissection can be used to obtain samples from tumor and normal tissues. See paragraphs 0306 or 0316.

The present specification and the state of the prior art at the time the application was filed indicate that the relative skill in the art in relation to the subject matter to which the claimed

invention pertains was high. At that time the application was filed, it was routine for a person skilled in the art to use recombinant DNA methods to determine the differential expression of, for example, threonine endopeptidase nucleic acids or products comprising or encoded by SEQ ID NOS:150, 152 or154 or a nucleic acid sequence with at least 95% homology with SEQ ID NOS: 150, 152 or 154 or threonine endopeptidase protein in tissue samples.

As provided in the specification, it was also routine for one skilled in the art to be able to test threonine endopeptidase nucleic acids or their products for diagnosing cancer. Various means for diction of CA gene's nucleic acid product expression are disclosed in the specification at paragraphs 0074 to 0092. Various means for diction of CA gene's encoded protein expression are disclosed in the specification at paragraphs 0093-0133. Thus the specification not only taught that threonine endopeptidase nucleic acids and expression products can be used to diagnosing cancer; but it also provided detailed support for a skilled artisan to carry out the claimed methods for diagnosing cancer.

The response has been considered but is not found to be persuasive for the following reasons:

Although it is routine in the art to detect the level of a nucleic acid in a cancer tissue, the art does not teach that the nucleic acid of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, or a genus of at least 95% or 98% variants thereof differentially express in colon cancer tissue or in colon tissue of patients at risk of colon cancer, as compared to non-cancerous colon tissue.

Further, although it is routine in the art to mutagenise a nucleic acid, the art does not teach structure of at least 95% or 98% variants of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, wherein said variants have the function of a threonine endopeptidase.

The response asserts as follows:

Factor 5: The presence of working examples.

The specification in paragraph 0300, provides an example in which the RT-PCR method can be used for analysis of differentially expressed gene. See also Figures 2-4. In paragraph 0304, the specification provides an example of detection of elevated levels of cDNAs associated with cancer (e.g., threonine endopeptidase cDNA) using arrays. Methods for detection of CA sequences (e.g., threonine endopeptidase gene) in human cancer cells and tissues by way of hybridization are taught in Example 5, paragraph 0319. Furthermore, generation of antibodies against CA polypeptides (e.g., threonine endopeptidase polypeptide) is taught in Examples 7-8, paragraph 324-326. Various methods for detection of CA proteins (e.g., threonine endopeptidase protein) have also been taught in Examples 9-10, paragraphs 327-328.

The specification also teaches that "[c]omparing expression patterns of uncharacterized genes may provide clues to their function. High throughput analysis of expression of hundreds or thousands of genes can help in (a) identification of complex genetic diseases, (b) analysis of differential gene expression over time, between tissues and disease states, and (c) drag discovery and toxicology studies. Increase or decrease in the levels of expression of certain genes correlate with cancer biology. For example, oncogenes are positive regulators of tumorigenesis, while tumor suppressor genes are negative regulators of tumorigenesis. (Marshall, Cell, 64:313-326

(1991); Weinberg, Science, 254:1138-1146 (1991))." See paragraph 0008. The specification also provides means for detection of cancer profile and correlating the expression levels of CA genes (e.g., threonine endopeptidase) to the cancer phenotype. See paragraphs 0161-0175. Therefore, in view of the extensive teachings and exemplifications provided in the specification, a skilled artisan could have reasonably correlated the in vitro effects of the claimed methods to their in vivo utility in providing means for diagnosing cancers.

The response has been considered but is not found to be persuasive for the following reasons:

The specification does not have any data or objective evidence that the nucleic acid of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, or a genus of at least 95% or 98% variants thereof differentially express in colon cancer tissue as compared to non-cancerous colon tissue. There are not data or objective evidence from retroviruse tagging indicating the nucleic acid of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, or a genus of at least 95% or 98% variants thereof differentially express in colon cancer tissue as compared to non-cancerous colon tissue.

Paragraphs 300 and 304 in the specification only disclose routine methods for detecting elevated levels of cDNAs associated with cancers. Paragraphs 300 and 304 do not disclose any data showing that the nucleic acid of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, or a genus of at least 95% or 98% variants thereof differentially express in colon cancer tissue as compared to non-cancerous colon tissue. In **figures 2-4**, there are **no data for the level** of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154 **in cancerous colon tissue** as compared to that in non-cancerous colon tissue. In figures 2-4, **no colon cancer tissues** or colon

tissue of patients at risk of colon cancer as samples are recited, and it is not clear in figures 2-4, **which target genes are detected**. Moreover, the data in figures 2-4 only disclose average threshold cycle values for PCR for target genes as compared to **housekeeping genes** (figures 2-4 legends on page 5 of the specification). There are **no data for the level of** SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154 **in non-cancerous colon tissue,** which level is not predictable and would not be predictably the same as that of housekeeping gene average.

Further, the specification, including figures 2-4, do not have any data or objective evidence that the nucleic acid of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, or a genus of at least 95% or 98% variants thereof are differentially express in colon tissue of patients at risk of colon cancer tissue as compared to non-risk patients.

Further, the specification does not teach how to make the claimed genus of at least 95% or 98% variants such that they have the same property, or the same function such as threonine endopeptidase, as that of SEQ ID NO:150, SEQ ID NO: 152 and SEQ ID NO: 154.

The response asserts as follows:

Factors 6 and 7: The quantity of experimentation necessary to make or use the invention and the amount of direction or guidance presented in the application.

The person of ordinary skill in the art would be able to practice the claimed invention following the guidance of the specification, using no more than routine experimentation. Threonine endopeptidase nucleic acids and techniques suitable for detecting their differential expression in a subject tissue and comparing it to a control such as non-cancerous colon, stomach or prostate tissure were known in the art at the time the application was filed. The specification

further provides detail information for a skilled person to carry out the claimed method. See the information provided in Example 2 for analysis of quantitative RT-PCR: comparative CT method; Example 3 for detection of elevated levels of cDNA associated with cancer using arrays; Example 4 for detection of CA-sequences in human cancer cells and tissues; Example 5 for detection of CA sequences in human cancer cells and tissues; Example 6 for expression of cloned polynucleotides in host cells; Example 7 for generation of antibodies against polypeptides; Example 8 for generation of monoclonal antibodies against a CA polypeptide; Example 9 for ELISA assay for detecting CA related antigens; Example 10 for identification and characterization of CA antigen on cancer cell surface; Example 13 for diagnostic imaging using CA specific antibodies; and Example 14 for immunohistochemical methods disclosed.

Thus, the specification teaches the person of skilled in the art that differential expression of CA genes (including threonine endopeptidase gene) and their products for diagnosing cancers are reliable and that detection of the differential expression leads to diagnosis of cancer. Accordingly, the specification provides ample guidance regarding the structure-function of threonine endopeptidase expression to enable any person skilled in the art to make or use the claimed methods without undue experimentation.

The response has been considered but is not found to be persuasive for the following reasons:

The specification only discloses routine methods in the art for detecting the level of a nucleic acid in a sample.

The specification, however, does not have any data or objective evidence that the nucleic acid of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, or a genus of at least 95% or

98% variants thereof differentially express in colon cancer tissue as compared to non-cancerous colon tissue. There are not data or objective evidence from retroviruse tagging indicating the nucleic acid of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, or a genus of at least 95% or 98% variants thereof differentially express in colon cancer tissue as compared to non-cancerous colon tissue.

Further, the specification does not have any data or objective evidence that the nucleic acid of SEQ ID NO:150, SEQ ID NO: 152 and/or SEQ ID NO: 154, or a genus of at least 95% or 98% variants thereof are differentially express in colon tissue of patients at risk of colon cancer tissue as compared to non-risk patients.

Further, the specification does not teach how to make the claimed genus of at least 95% or 98% variants such that they have the same property, such as three-dimensional structure necessary for the function as threonine endopeptidase, or the same function such as threonine endopeptidase, as that of SEQ ID NO:150, SEQ ID NO: 152 and SEQ ID NO: 154.

It would be undue experimentation for one to practice the claimed method, in view that absence of objective evidence, one cannot predict that whether the level of the nucleic acid SEQ ID NOs: 150, 152 and /or154 or its at least 95% or 98% variant is different in colon cancer tissues or in colon tissue of a patient at risk of colon cancer, as compared to non-cancerous colon tissues, because the level of expression of a polypeptide in a tissue, including cancer tissue, is not predictable, in view of the teaching of Stanton et al, and Iehle et al, all of record.

The response asserts as follows:

Factor 8: The predictability or unpredictability of the art.

Applicants submit that the claims are directed to determining the difference in expression between the claimed sequences or those that are 95% or 98% identical to recited SEQ ID NOS. Accordingly, the level of expression is immaterial. Rather, it is the comparison as described previously above and taught throughout the application. Moreover, even if the Office's assertion applied to the claimed invention, Applicants respectfully point out that the patent statutes do not require absolute predictability, only that it would not require undue experimentation to make and use the claimed invention.

In view of the foregoing arguments, Applicant submit that claims 49, 56-63, 66-72 and 75-86 are enabled because, in view of state of art, teachings and exemplifications provided in the application, a person of ordinary skill in the art could make or use the claimed methods without undue experimentation.

The response has been considered but is not found to be persuasive for the following reasons:

MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is

unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

The art here is highly unpredictable.

In the absence of objective evidence, one cannot predict whether the level of the nucleic acid of SEQ ID NOs: 150, 152 and /or 154 is **different** in colon cancer tissues as compared to non-cancerous colon tissues, because the level of expression of a polypeptide in cancer tissue is not predictable and it is well known in the art that not every gene in a cancer cell is affected in carcinogenesis, such as mutation or changes in expression as compared to normal control cells, in view of the teaching of Stanton et al, Iehle et al, and Abbaszadegan et al, all of record.

Moreover, even if SEQ ID NO: 150, SEQ ID NO:152 and/or SEQ ID NO:154 could be used for diagnosis of colon cancer, one cannot predict that its **variants**, including its **95% or 98% variant,** or **the proteasome C7-I** nucleic acid, as recited in claims 56-58, 60-63, 66-70, 75-76, 78, 80-81, 83, 84-86 could be used for diagnosis of colon cancer, because it is well known in the art that variants of a sequence do not necessarily express at the same level as the corresponding wild type, in view of the teaching of Schmid et al, and Conner et al, all of record.

Further, without validation of the claimed method, as claimed in claim 60, one cannot predict that the claimed differential expression of the proteasome C7-I nucleic acid indicates **predisposition to or risk** of colon cancer, in view of the teaching of Tockman et al, Oesterreich et al, Vandersompele et al, all indicating that prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials.

Moreover, one cannot predict that the claimed method could be used successfully for detecting colon cancer, when the **control is any tissue type other than colon tissue**, as claimed in claim 49, or **any control**, as claimed in claim 61, or any **non-cancerous control**, as claimed in claim 72, because the level of SEQ ID NO: 150, SEQ ID NO:152 or SEQ ID NO:154 in these tissues is unpredictable, in view of the teaching of Stanton et al, and Iehle et al, all of record, and thus would not predictably to be different from that in colon cancer tissue.

Moreover, one cannot predict that the claimed method could be used successfully for detecting colon cancer, when the control is "**normal" colon**, as claimed in claim 67, because it is not clear what constitutes a normal colon, which is not necessarily non-cancerous, and the level of the claimed nucleic acid in which is not predictable, in view of the teaching of Stanton et al, Iehle et al, and Abbaszadegan et al, all of record.

In addition, one cannot predict the structure the claimed **gene**, as claimed in claim 49, because the art indicates that the structures of genes with naturally occurring regulatory elements and untranslated regions is empirically determined, as taught by Harris et al, Ahn et al, and Cawthon et al, all of record.

Further, on cannot predict that the claimed method, as claimed in claims 72, 86, would be specific and would not detect unrelated sequences with unknown properties, because "a **complement**" is reasonably interpreted as full length or partial complement, wherein a partial complement needs to be complementary only to a few nucleotides of SEQ ID NO: 150, SEQ ID NO:152 or SEQ ID NO:154.

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the

claimed invention, there would be an undue quantity of experimentation required for one of skill in the art to practice the claimed invention, that is commensurate in scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 61-63, 67, 69, 83, 86 remain rejected under 35 U.S.C. 102(e) as being anticipated by Tang et al (US20030219745A1, filed on April, 11, 2002), for reasons already of record in paper of 12/05/08.

The response asserts as follows:

In contrast to the Examiner's assertion, the cited passage fails to teach that any of the polypeptides of the invention can be used for diagnosis of cancer nor does it specifically teach that SEQ ID NO: 124 can be used for diagnosis. Rather, the cited paragraph speculates that some of the sequences might be amenable for use in diagnosis. Tang et al. describe 411 sequences and characterizes them as possibly being involved in cancer or possibly being useful for the diagnosis or prognosis of one or more types of cancer. Out of these 411 sequences Tang et al. fails to teach that SEQ ID NO: 124 is involve in cancer or that it can be used for the diagnosis of cancer. Similarly, Tang et al. also does not teach that SEQ ID NO: 124 is specifically involved with

colon, stomach or prostate cancer or that it can be used for the diagnosis of colon, stomach or prostate cancer. Absent such certainty, Tang et al. is speculative and fails to anticipate the invention as claimed.

The response has been considered but is not found to be persuasive for the following reasons:

This is 102 rejection, and the enablement issue is not germane here (see 102 statute).

Further, SEQ ID NO:124, which is 98% similar to SEQ ID NO:154 of the claimed invention, clearly is included in the sequences for use to detect cancers, including colon cancer, taught by Tang et al.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
August 18, 2009

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643